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Preservation of Recurrent Laryngeal Nerve Invaded by Differentiated Thyroid Cancer

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Objective

This study was undertaken to determine whether the recurrent laryngeal nerve involved in differentiated thyroid carcinoma could be preserved.

Summary Background Data

Few investigations have provided definitive results concerning preservation of the recurrent laryngeal nerve involved in thyroid cancer. Complete excision with resection of the recurrent laryngeal nerve reportedly did not improve survival over incomplete excision in differentiated thyroid carcinoma.

Methods

A retrospective study was performed with the medical records of 50 patients with differentiated carcinoma and preoperative normal vocal cord function to investigate outcomes of recurrent laryngeal nerve preservation including local recurrence, prognosis, and postoperative vocal cord function. The recurrent laryngeal nerves on 1 or both sides were preserved in 23 patients (the preserved group), whereas the involved recurrent laryngeal nerve of the other 27 patients was resected (the resected group).

Results

Backgrounds of patients were similar between the resected and preserved groups. The number of patients with recurrences in each group was similar, and incidence of local, regional, and distant metastatic recurrences were not different between the groups. Postoperative overall survival of the preserved group was similar to that of the resected group ($p = 0.1208$). More than 60% of patients or of nerve at risk in the preserved group restored normal vocal cord function within 6 months. Some functional vocal cord movement was recognized in 80% of patients or of nerve at risk. All patients in the resected group including patients with nerve anastomosis showed permanent paralysis of the ipsilateral vocal cord.

Conclusions

These results suggested that the recurrent laryngeal nerve, even if infiltrated by differentiated thyroid cancer, is worthwhile to preserve for maintenance of postoperative vocal cord function without affecting the incidence of local recurrence or prognosis.

Differentiated carcinoma of the thyroid gland is a predominantly curable disease and has a low mortality rate.[1] Thus, the major concern in thyroid surgery is morbidity, which includes hemorrhage, hypoparathyroidism, and damage to the recurrent laryngeal nerve.[2] Among these complications, recurrent laryngeal nerve palsy is the most feared by both patient and surgeon.[3,4] The incidence of recurrent laryngeal nerve palsy after thyroid or parathyroid surgery was reportedly from 0% to 14%.[4,5] These rates may change dependent on underlying diseases, nerve at risk, operative procedures, and permanent or transient palsy.[4,5]

Invasion of regional structures by differentiated papillary or follicular carcinoma of the thyroid gland is basically infrequent. Sixteen percent of papillary thyroid carcinomas were reported to have invasion into surrounding tissues including muscles, larynx, trachea, the recurrent laryngeal nerve, or esophagus.[6] The cause of death from papillary carcinoma, however, was related to uneradicated local disease in 36% to 47%.[6,7] Some reports have suggested that resectional management of these thyroid cancers improved prognosis of patients with locally invasive thyroid cancer.[8,9]

In locally advanced thyroid cancer, the recurrent laryngeal nerve frequently is involved in both tumors. Many experienced surgeons routinely advocate avoiding recurrent laryngeal nerve injury or resection. However, when the nerve obviously is infiltrated by the cancer, a surgeon must decide whether to sacrifice it or to free it from its restrictions in an attempt to keep function at any cost. Some surgeons are aggressive to sacrifice the involved nerve for complete excision.[3] Others, however, have suggested that complete excision with resectional management of the recurrent laryngeal nerve did not improve survival when differentiated thyroid carcinoma infiltrates into the nerve.[12] A few reports have suggested that preoperative recurrent laryngeal nerve palsy can recover function after surgery, even when the nodule is malignant.[10–12] These results suggested that preservation of the nerve regardless of preoperative vocal cord function may improve morbidity of patients. However, they did not describe details of local and regional recurrences and postoperative function of the ipsilateral vocal cord.

In the current study, we performed a retrospective study to investigate the importance of preservation of the nerve involved in the differentiated thyroid cancer with special reference to local recurrence, prognosis, and postoperative function of the nerve. Although the current study was retrospective and of a nonrandomized design, our results may be of clinical value to endocrinologists because evaluation of differentiated thyroid cancer requires long-term follow-up. The results suggested that preservation of the nerve improved postoperative vocal cord function and did not change rates of local recurrence and mortality.

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PATIENTS AND METHODS

Patients

Patient Profiles

From 1980 to 1995, 242 patients with primary or recurrent differentiated thyroid cancer underwent surgery at the First Department of Surgery, Osaka University Medical School, and its affiliated hospitals, Osaka Police Hospital and Kure National Hospital. Ninety-eight of these 242 patients had differentiated thyroid cancer with invasion into the surrounding tissues. Fifty of 98 patients before surgery showed intact vocal cord movement and had tumors intraoperatively proved to have invaded into the recurrent laryngeal nerve on either one or both sides. Four patients with preoperative recurrent laryngeal nerve palsy caused by cancer invasion were excluded from this study because the incidence of functional recovery of the vocal cord in these patients seems to be different from that in subjects without palsy. Fifty patients with sufficient medical records and surgical materials were studied retrospectively. The subjects were 14 men and 36 women, and their age at diagnosis was 61 ± 12 years (mean ± standard deviation). Forty-one patients had primary thyroid cancer and 9 patients recurrent. Seven patients had no lymph node metastasis, and the other 43 patients had various degrees of lymph node metastasis. Distant metastasis was evident in seven patients at diagnosis: lung metastasis in six, and lung and bone metastases in one. The other patients were free from distant metastasis at diagnosis. Thirty-two patients were alive on January 1, 1996, and 18 patients died during the follow-up period. Among these 18 patients, 11 died of thyroid cancer, 6 of unrelated causes, and 1 of postoperative complications. The mean follow-up period was 6.3 years.

Operative Methods

Our usual approach to surgery for thyroid cancer is complete resection of the thyroid tumor by lobectomy plus isthmectomy or total thyroidectomy and central cervical plus ipsilateral jugular lymph node dissection when a tumor is limited to one lobe. When tumors are present in both lobes, total thyroidectomy and central cervical plus bilateral jugular lymph node dissection usually are performed. Among the 50 patients described here, 20 underwent unilateral lobectomy plus isthmectomy and 30 underwent total thyroidectomy. Isolation of the recurrent laryngeal nerve from thyroid cancer mainly was per-

formed by sharp dissection to leave as little tumor as possible. However, a minimum microscopic or macroscopic tumor might remain anywhere along the course of the preserved recurrent laryngeal nerve. Recurrent laryngeal nerves of two patients were isolated partly using either an ultrasonic or an electric scalpel, and their ipsilateral vocal cord showed permanent paralysis. All patients routinely received thyroid-stimulating hormone suppression therapy after surgery, and no patients received prophylactic use of radioiodine.

Groups

The 50 patients were divided into the 2 groups: the resected group and the preserved group. The preserved group consisted of 23 patients whose involved recurrent laryngeal nerve on 1 or both sides was isolated from tumors and was preserved. The remaining 27 patients, in whom the recurrent laryngeal nerve involved in tumors was resected, comprised the resected group.

Recurrent Laryngeal Nerve Function

Function of the recurrent laryngeal nerve was assessed by otolaryngologists using a laryngoscope because patients may have vocal cord paralysis without changes in their voice. Postoperative function of the nerve was graded in this study as follows: permanent paralysis, vocal cord paralysis was persistent for more than 6 months; partial improvement, ipsilateral vocal cord showed paralysis during the perioperative period and its movement showed incomplete recovery within 6 months; transient, ipsilateral vocal cord with paralysis or limited movement during the perioperative period recovered completely within 6 months; functioning, ipsilateral vocal cord retained normal movement after surgery.

The recurrent laryngeal nerves on both sides were involved in the cancer in seven patients. Two patients in the resected group underwent total thyroidectomy plus laryngotracheal resection and one underwent total thyroidectomy then tracheostomy. The recurrent laryngeal nerves on both sides in two patients of the preserved group were left unresected. Of three patients in the preserved group, the recurrent laryngeal nerve on one side was preserved and that on the other side was resected. Three nerves in the resected group were resected and reconstructed. When evaluating postoperative nerve function in each patient, nerve function on the better side was used for functional grading.

Methods

Histologic Type and Subtype

The final histologic diagnoses were 5 follicular and 45 papillary carcinomas. The differentiated thyroid cancers were further classified into poorly or well-differentiated carcinoma according to the criteria of Sakamoto et al.[13] Briefly, the characteristic histology of a poorly differentiated carcinoma was the presence of a solid, trabecular or scirrhous pattern or both.[13] Twenty-seven tumors were well-differentiated carcinomas and 23 were poorly differentiated.

Statistical Analysis

Fisher's exact test, chi square test, and Kaplan–Meier method for postoperative survival with log–rank test were used for statistical comparisons. The relative importance of the various prognostic factors for postoperative survival as identified by multivariate analysis was analyzed using Cox's proportional hazards model.[14] All statistical analyses were performed using a commercially available personal computer program, SPSS (SPSS, Chicago, IL).

RESULTS

Backgrounds of patients in the resected and preserved groups were compared according to several prognostic factors and risk factors for recurrence reported previously.[15] The mean age in the resected group (63 ± 9) was not different from that in the preserved group (58 ± 14). All other factors including gender, operative methods, lymph node involvement, the presence of distant metastasis at diagnosis, histology, and histologic differentiation were similar between the two groups (Table 1). The extent of local invasion was further evaluated. As listed in Table 1, the incidences of invasion into the trachea, esophagus, carotid artery, jugular vein, anterior cervical muscles, sternocleidmastoid muscle, or phrenic nerve were not significantly different between the groups. Residual tumors other than the recurrent laryngeal nerve also were not significantly different between the two groups (Table 1). These results suggested that the two groups had similar backgrounds and local, regional, and distant extensions except preservation of the recurrent laryngeal nerve.

The incidence of postoperative recurrence was not different between the two groups (Table 2). Rates of local, regional, and distant metastatic recurrences also were similar between the groups.

The postoperative prognosis was compared between groups. Fourteen patients in the resected group were alive on January 1, 1996, and 13 patients died during the follow-up period. Eleven of 13 patients died of thyroid cancer, one of unrelated causes, and one of postoperative complications. Conversely, 18 patients in the preserved group were alive, and five patients died of unrelated causes during the follow-up period. Thus, prognosis of the preserved group appeared to be relatively better than that of the resected group (Table 2). When postoperative

Table 1. PATIENT BACKGROUNDS

	Resected (n = 27)	Preserved (n = 23)	p Value
Age (yr)	63 ± 9	58 ± 14	0.1542
Gender			
Male	8	6	>0.9999
Female	19	17	
Surgery			
Primary	20	21	0.1519
Secondary	7	2	
Operation			
Lobectomy	16	7	0.1578
Total	13	16	
Lymph node metastasis at diagnosis			0.4295
(−)	5	2	
(+)	22	21	
Distant metastasis at diagnosis			0.4295
(−)	22	21	
(+)	5	2	
Histology			
Papillary	23	22	0.3573
Follicular	4	1	
Differentiation*			
Well	11	16	0.0515
Poorly	16	7	
Invasion into other tissues			
Trachea	15 (56%)	13 (57%)	>0.9999
Esophagus	12 (44%)	5 (22%)	0.1356
Carotid artery	0 (0%)	2 (9%)	0.2065
Jugular vein	13 (48%)	11 (48%)	>0.9999
ACM†	17 (63%)	14 (61%)	>0.9999
SCM‡	6 (22%)	1 (4%)	0.1068
Phrenic nerve	2 (7%)	0 (0%)	0.4931
Local residual cancer§	3 (11%)	4 (17%)	0.6888

* Histological differentiation was determined according to Sakamoto et al.[13]
† Invasion into anterior cervical muscles.
‡ Invasion into the sternocleidomastoid muscle.
§ Positive local residual cancer other than along the recurrent laryngeal nerve. The numbers of patients with macroscopically suspected residual cancer are indicated.

Table 2. POSTOPERATIVE RECURRENCE PROGNOSIS

	Resected (n = 27)	Preserved (n = 23)	p Value
Recurrence			
Total cases with recurrence	12 (44%)	8 (35%)	0.5691
Site of recurrence			
Local	3 (11%)	3 (13%)	>0.9999
Regional	10 (37%)	4 (17%)	0.2060
Distant	9 (33%)	3 (13%)	0.1119
Prognosis			
Alive	14	18	0.0773
Dead	13	5	

survival was compared by the Kaplan–Meier method (Fig. 1), overall survival was not different between the two groups (p = 0.1208). Mean postoperative survival periods of the resected and preserved groups were 8.55 ± 1.17 and 10.23 ± 1.04 years, respectively. Multivariate analysis using Cox's proportional hazard model was performed with data from the 50 patients, and both age (p = 0.0187) and invasion into the trachea (p = 0.0320) were indicated to be independent prognostic factors with odds ratios of 1.129 and 11.660, respectively. Gender, lymph node involvement, distant metastasis at diagnosis, histology, differentiation, operative methods, invasion into surrounding tissues, incomplete resection, and preservation of the recurrent laryngeal nerve were not independent prognostic factors. These results indicated that preservation of the recurrent laryngeal nerve involved in differentiated thyroid cancer did not adversely affect postoperative survival of patients.

Postoperative function of the recurrent laryngeal nerve isolated from the cancer was evaluated (Table 3). Of twenty-three patients in the preserved group, 4 had permanent paralysis of the ipsilateral recurrent laryngeal nerve. In two of four patients, the nerve was isolated from the tumor partly using an ultrasonic or an electric scalpel. In four patients, movement of the ipsilateral vocal cord recovered partially within 6 months. Six patients showed complete recovery after transient paresis, and eight showed normal function. Vocal cord function of one patient, whose voice was unchanged after surgery, had not been assessed by an otolaryngologist.

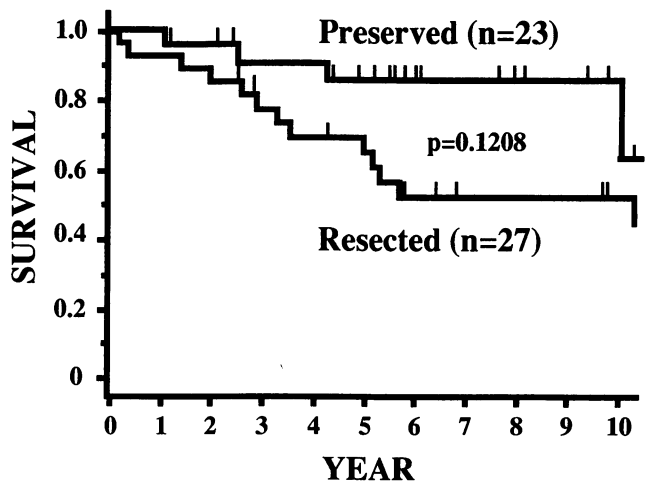

Figure 1. Overall postoperative survival in the resected and preserved groups. Overall postoperative survival was compared between the resected and preserved groups using the Kaplan–Meier method. There were no significant statistical differences between the two groups (p = 0.1208).

Table 3. OUTCOME OF PRESERVED RECURRENT LARYNGEAL NERVE AFTER SURGERY

	Number of Patients (%)	Nerve at Risk (%)
Permanent paralysis	4 (17)	4 (16)
Partial improvement*	4 (17)	5 (20)
Transient†	6 (27)	7 (28)
Functioning‡	8 (35)	8 (32)
Unknown function	1 (4)	1 (4)
Total	23 (100)	25 (100)

* Ipsilateral vocal cord showed paralysis after surgery, and its movement improved partially within 6 months but the cord had limited movement.
† Ipsilateral vocal cord showed paralysis or limited movement during perioperative periods, and its movement became normal within 6 months.
‡ Movement of ipsilateral vocal cord was normal after operation.

As both sides of the recurrent laryngeal nerve were preserved in two patients, a total 25 were nerve at risk. When postoperative nerve function was evaluated according to nerve at risk, permanent paralysis, partial improvement, transient, and functioning were 4, 5, 7, and 8, respectively (Table 3). These results indicated that 80% of patients or of nerve at risk showed restored vocal cord function in the preserved group. Three nerves resected and reconstructed showed no functional recovery of the ipsilateral vocal cord. Thus, the vocal cords in all patients showed permanent paralysis in the resected group.

DISCUSSION

The reported incidence of recurrent laryngeal nerve palsy varies, and up to 50% of recurrent laryngeal nerve palsy is transient.[4] The risk of permanent paralysis to the recurrent laryngeal nerve has been described to be $<1\%$ in experienced surgeons.[2,5] However, these rates also may be influenced by underlying diseases and nerves at risk.[4] These features makes it difficult to make meaningful comparisons between the reports. In the current study, we retrospectively studied postoperative vocal cord function, local failures and prognosis of patients with intact preoperative vocal cord movement, and differentiated thyroid carcinoma invading into the recurrent laryngeal nerve.

Few authors have provided definitive data or guidance in reference to intentional sacrifice of the recurrent laryngeal nerve when involved in thyroid cancer.[3] Falk and McCaffrey[12] reported recently that complete excision with resection of the recurrent laryngeal nerve did not improve survival over incomplete excision, when papillary thyroid carcinoma infiltrates into a functioning recurrent laryngeal nerve. They recommended preservation of the recurrent laryngeal nerves, even if excision is incomplete. However, their study did not describe the restoration rate of recurrent laryngeal nerve function and postoperative local failures. As complete excision of differentiated thyroid cancer with extrathyroidal extension was reported to have better prognosis than incomplete excision,[8,15,16] others are more aggressive in sacrificing the involved nerve.[3] Thus, the issue regarding management of involved recurrent laryngeal nerve in differentiated thyroid cancer is not entirely clear. We have used conservative treatment for these recurrent laryngeal nerves for more than a decade. The current investigation showed that preservation of the recurrent laryngeal nerve, whenever possible if vocal cord function is normal before surgery despite anatomic involvement with differentiated thyroid cancers, did not increase local or regional recurrence and did not result in poor prognosis compared with that of complete resection.

Because this study was retrospective and not randomized, there may have been bias between the two groups. For example, the background of the two groups might be different, and it is possible that the resected group may have had more advanced cancer than the preserved group. This possibility was evaluated in this investigation using incidence of lymph node and distant metastases at diagnosis and incidence of invasion into surrounding tissues. As listed in Table 1, cancers in the two groups appeared to have similar regional and distant metastatic states, and similar local expansion. The rates of incomplete excision outside the recurrent laryngeal nerve also were similar (Table 1). These results suggested that the two groups are postulated to have similar backgrounds.

Reported 5-year survival rates of patients with thyroid cancer invading the upper aerodigestive system are 70% to 80%.[8,17,18] The local recurrence rate after complete resectional management for these thyroid cancers was reported to be 38%.[19] McCaffrey et al.[6] reported that 5-year and 10-year survival rates of patients with locally invasive thyroid cancer were 79% and 63%, respectively. Another report indicated that 10-year overall and disease-free survival rates were nearly 85% and 70%, respectively.[20] Andersen et al.[16] suggested that >40% of patients with locally invasive thyroid cancer suffered from local failures during the follow-up period of 30 years and their overall survival rates at 5 and 10 years were to be 60% and 50%, respectively. Our values for recurrence and overall survival were 40% and 64%, respectively, with a mean follow-up period of 6.3 years. Five- and 10-year survival rates of all patients in the current study were 70% and 60%, respectively. Local recurrence and survival rates of the preserved group were 35% and 78%, respectively. These values were comparable to reported values in thyroid cancer invading extrathyroidal tissues including the trachea.[6,8,9,16-20] Univariate and multivariate analyses indicated that preservation of the recurrent laryngeal nerve was not a prognostic factor in these settings (Fig. 1 and

Results section). Taken together, it is suggested that preservation of invaded recurrent laryngeal nerve did not increase local failure or mortality compared to resectional management.

Because most patients with thyroid cancer invading extrathyroidal tissues are in the high-risk group, total thyroidectomy and postoperative radioiodine ablation are strongly indicated for these patients.[21] A recent report has shown that treatment with radioiodine is the single most powerful prognostic indicator for disease-free survival and that radioiodine ablation significantly increased survival.[22] In fact, judicious, aggressive resection, although preserving function, is advocated for locally advanced thyroid cancer, and radioiodine ablation is useful in these settings if uptake is proved.[23] In Japan, however, radioiodine treatments could be done in a limited number of hospitals and clinics until recently. In the current investigation, only three patients received radioiodine therapy for newly developed postoperative pulmonary metastases. If total thyroidectomy combined with radioiodine ablation had been the treatment choice for patients in the current study, the postoperative recurrence rate and prognosis might be improved.

In the current study, patients with preoperative nerve palsy were not included because of unknown recovery rates of nerve function. However, a previous report indicated that recovery of vocal cord function may occur after thyroid surgery for benign diseases.[10,11] This recovery also was reported to occur even in malignant thyroid tumors, including differentiated carcinomas and malignant lymphoma.[12,24] Incomplete excision to preserve involved recurrent laryngeal nerve did not increase postoperative mortality.[12] Thus, recurrent laryngeal nerves invaded by differentiated thyroid carcinoma could be preserved without affecting the prognosis, even in the presence of poor vocal cord function before surgery. This problem, however, requires future investigations.

The other major problem related to nerve preservation, recurrent laryngeal nerve function after surgery, was evaluated with indirect laryngoscope or laryngeal fiberscope in the current study. Approximately 60% of patients in the preserved group showed restored normal vocal cord function within 6 months. Some functional movement of the vocal cord was recognized in 80% of patients, who had an almost normal voice in the distant postoperative period (data not shown). The restoration rate of recurrent laryngeal nerve function based on nerve at risk showed similar values. The restoration rate of vocal cord function was not 100%. This was partly caused by the surgical procedures that were performed to leave as little tumor as possible. These values may not be sufficient for experienced surgeons, and more meticulous sharp dissection may improve postoperative nerve function. However, these values are not considered to be extremely inferior to values reported previously of postoperative nerve paralysis in thyroid cancer surgery[3,5] if it is taken into consideration that the nerves in the current investigation had been freed from the cancerous restriction. The other method to retain functional integrity of the vocal cord is reconstruction of the resected recurrent laryngeal nerve. In this investigation, three nerves were resected and reconstructed, and no functional recovery of the ipsilateral vocal cord was observed. The vocal cords of all patients in the resected group showed permanent paralysis. Although a few authors reported complete recovery of resected and reconstructed recurrent laryngeal nerve, most previous reports suggested that nerve anastomosis was inadequate to restore normal laryngeal function but may prevent atrophic changes in the paralyzed muscles because of misdirected regeneration of the nerve.[3] Thus, preservation of the recurrent laryngeal nerve appears to be functionally superior to resection and reconstruction of the nerve.

In summary, we investigated local failures, prognosis, and postoperative vocal cord function in patients whose recurrent laryngeal nerves were involved in differentiated thyroid carcinoma. The results suggested that preservation of the nerve improved postoperative vocal cord function without affecting local recurrence or prognosis. The current investigation clearly indicated that involved recurrent laryngeal nerves may be preserved, at least if the nerve can be isolated from differentiated thyroid cancer.

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